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COMPUTER-ASSISTED DETERMINATION OF MINIMUM ENERGY CONFORMATIONS VI. A PHARMACOPHORE MODEL OF THE ACTIVE REGION OF THE ALPHA2-ADRENOCEPTOR

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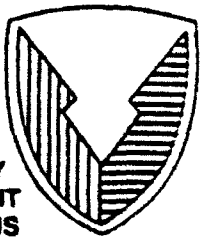
RESEARCH DIRECTORATE

September 1992



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Molecular modeling and computational chemistry techniques are used to analyze compounds in developing pharmacophores of biological receptors to use as templates in structure activity relationship studies and to design new chemicals having physiological activity of interest. In this study, the results of x-ray crystal analyses and PM3 semi-empirical molecular orbital conformational analyses are used to determine the three-dimensional representations of selected adrenergic compounds known to be agonists with the alpha2-adrenoceptor in achieving optimized geometries and electrostatic parameters. The alpha2-adrenergic agonists interact with the adrenergic system receptors to produce various increases or decreases in hemodynamic responses (i.e., hypertension, hypotension, bradycardia) and sedation. A pharmacophore model of the active region of the alpha2-adrenoceptor is described based on the superimposition of common structural, electrostatic, and physicochemical features of the compounds. Using the model to predict compound adrenergic activity and to design alpha2-adrenergic compounds is discussed.

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PREFACE

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1. INTRODUCTION

The adrenergic system is made up of a variety of receptor subtypes that have been differentiated into two main categories; alpha 1 and alpha 2.[1,2,3] The physiological responses of compounds interacting on the system vary from increases and decreases in cardiovascular (i.e., heart rate, blood pressure) and respiratory functions to the ability to cause sedation and anesthesia. Timmermans[4] and Savola[5] discuss the classification and mechanisms of action of compounds on the various types of adrenergic receptors; and Ruffolo[6] discusses structure-activity relationships (SAR) specifically with the alpha2-adrenergic system.

Alpha2-adrenergic agonists can be potent sedatives.[7,8] Most important, anesthesia and sedation are produced by these agonists without the unwanted side effect of respiratory depression. Because of this physiological response, a molecular modeling and theoretical chemistry study was performed to develop a "pharmacophore model" of the alpha2-adrenergic receptor (adrenoceptor) active region for use in SAR studies and as a template in designing compounds having desired sedative and anesthetic activity. A proposed topography of the active region of the alpha2-adrenoceptor (A2AR) is defined.

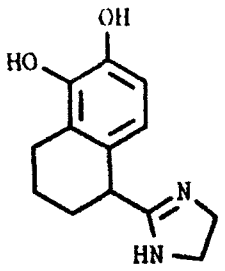
2. EXPERIMENTATION

2.1 Compound Structures.

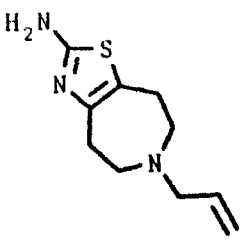
Fourteen compounds known to interact as agonists at the A2AR are analyzed. The compounds (Figure 1) are BHT920,[3] BHT933,[3] Clonidine,[4] M-7,[4] Guanabenz,[4] Guanfacine,[4] UK14304,[4] Medetomidine,[7] Noradrenaline,[9] Alpha-methylnoradrenaline,[9] YAII085,[10] the stereoisomers of R-2-(5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline [A62032 (S)[11] and A62033 (R)[11]] and Moxonidine.[12] The compounds represent 10 different classes that are composed of planar ring (mostly aromatic) and various nitrogen environments.

2.2 Three-Dimensional Minimum Energy Conformation Optimization.

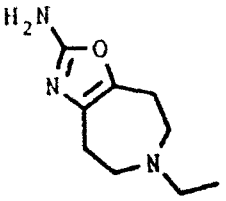
The Chemometric/Biometric Modeling Branch, Research Directorate, U.S. Army Chemical Research, Development and Engineering Center (CRDEC) Molecular Modeling Analysis and Display System (MMADS) (Version 3.1)[13] was used to incorporate the structures and perform the minimum energy and semi-empirical molecular orbital calculations.



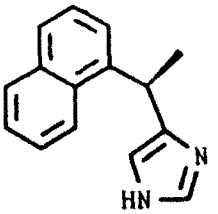
A62032 (S)
A62033 (R)



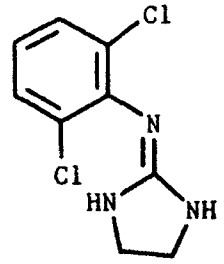
BHT920



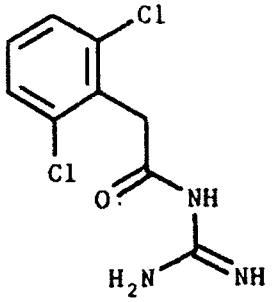
BHT933



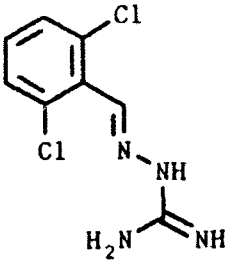
YAI1085



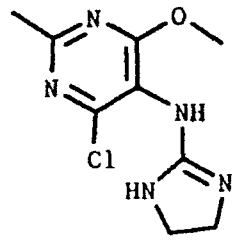
Clonidine



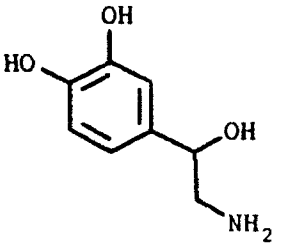
Guanfacine



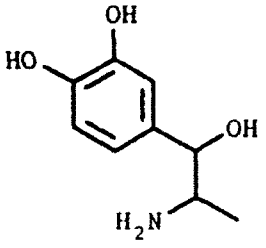
Guanabenz



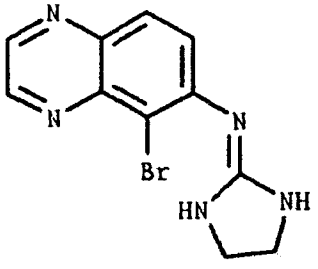
Moxonidine



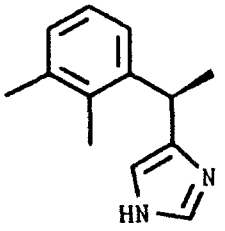
Noradrenaline



Alphamethylnoradrenaline



UK14304



Medetomidine

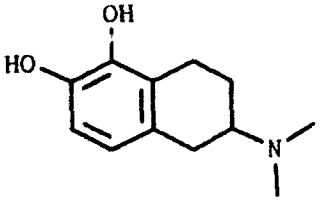


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Figure 1. Alpha2-Adrenergic Agonists Analyzed

In the initial analysis, x-ray crystal coordinates were used for the following three compounds: noradrenaline,[14] clonidine,[15] and A62032.[11] The three-dimensional conformations of these compounds were used as templates to construct and incorporate the other compounds for MMADS three-dimensional conformation analysis. As the study progressed, the crystal structure (Unpublished results, 1991, Laboratory for the Structure of Matter, Naval Research Laboratories, Washington, DC) of YAII085 was obtained. This structure was used in developing the final pharmacophore model.

Initially, conformational minimum energy calculations were performed to achieve molecular mechanics structure optimization[16] (optimized geometries) using the empirical MM2 (Quantum Chemistry Program Exchange version dated 1980) computer program developed by Allinger and Yuh.[17]

Next, the MM2 Cartesian coordinates of each compound were used as starting coordinates for input into the MOPAC[18] program for determining the molecular orbital optimized geometries of the unprotonated and protonated forms of each compound using the PM3 Hamiltonians.

The PM3 coordinates were then used as starting coordinates for MOPAC AM1[18] calculations. A Digital Equipment Corporation (Maynard, MA) MicroVax II within a VMS operating system environment was used for the calculations.

2.3 Alpha2-Adrenoceptor Pharmacophore Development.

Identifying of the three-dimensional stearic (geometric), physicochemical, and electrostatic parameters to be evaluated involved consultations with experts, literature searches, and analyses of compounds known to interact with the adrenergic system. Studies,[1,3,10,11,19,20] especially those by Timmermans,[4] Savola,[5] Ruffolo,[6,7,21] and Hancock,[22] suggest specific structural and functional group requirements for compound interaction with the A2AR.

The MMADS was used to incorporate and manipulate (STICK option) the compounds. The Tektronix 4105 series color graphics computer terminal to graphically displayed the 14 structures and performed a molecular modeling analysis.

The crystal structure coordinates of noradrenaline, clonidine, and A62032 were used in all molecular modeling analyses (MM2, PM3, AM1).

Initially, the 3 crystal structures and the 11 unprotonated MM2 optimized structures were superimposed on each other with the common planar ring carbons overlapped. The MM2 optimized structure of the compound Medetomidine (R-form) was used as the starting molecule to which all others were oriented. The procedure was to superimpose a molecule to the "best" three-dimensional fit of the molecule's planar ring carbons and its nitrogen to that of Medetomidine's and then save the two overlapped molecules as the template for the next compound to be added. The next compound was added to the two compounds and overlapped similarly, and the three-compound overlap became the new template for the next compound to be added. This procedure

was reiterated until all 14 compounds were overlapped. As compounds were added, compound functional regions and geometric positions of common compound atoms were identified. The above process was reiterated, incorporating the identified common attributes until an initial pharmacophore model was developed.

The same procedure was followed using the AM1 and PM3 optimized geometries. After analysis, the compounds were then protonated at the nitrogen predicted to interact with the adrenoceptor and optimized for their protonated three-dimensional conformations. The same overlap procedure was used on the protonated PM3 and protonated AM1 optimized geometries.

In the final analysis, the crystal structure of YAII085 replaced its PM3 and AM1 protonated structures. The final adrenoceptor pharmacophore was developed from the overlap of the 10 PM3 protonated structures and the 4 crystal structures.

3. RESULTS

3.1 Three-Dimensional Conformations of Selected Alpha2-Adrenergic Compounds.

The individual compound structure files, which list the 10 PM3 program calculated three-dimensional Cartesian atom coordinates corresponding to the minimum energy optimized geometry for the protonated conformations and the 4 x-ray crystal Cartesian atom coordinates that were used to determine the A2AR, are reported in Appendix B.

3.2 Alpha2-Adrenoceptor Pharmacophore Model (A2ARPHar).

Figures 2 and 3 (compounds rotated 90°) illustrate the results of the molecular modeling analysis of the overlap of the 14 A2AR agonists. Two regions (A, a planar ring system generally aromatic in functionality, and B, a region containing a nitrogen atom and its proton) are common to each agonist and are (or can be) positioned so that they overlap. A third region (C, although not common to all the compounds) may involve the interaction of the hydroxyl groups of A62032, A62033, noradrenaline, and alphamethylnor-adrenaline.

Figures 4 and 5 illustrate the topography and give the three-dimensional coordinates of a proposed A2ARPHar model developed from the overlap of the above compounds. The model identifies the following four distinct potential compound/receptor interaction regions: (a) Region A is a planar region that may involve lipophilic or pi-pi interactions; (b) Region B consists of an environment for compound proton/receptor interaction; (c) Region C is a region that provides potential interaction with a compound's hydroxyl or negatively charged functional groups. Region C may not exist in the A2AR subtype that produces sedation. However, there is insufficient data to eliminate region C; therefore, the model includes this region for use as an area to be studied in future research efforts. Region D is depicted in the

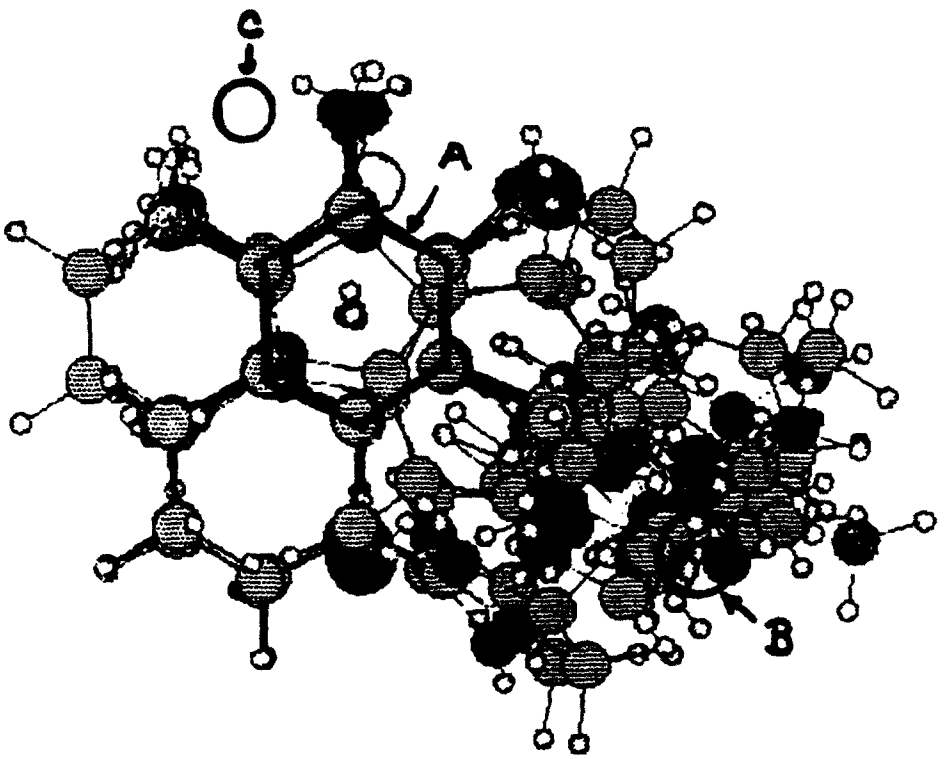


Figure 2. Overlap of 14 Alpha2-Adrenergic Agonists

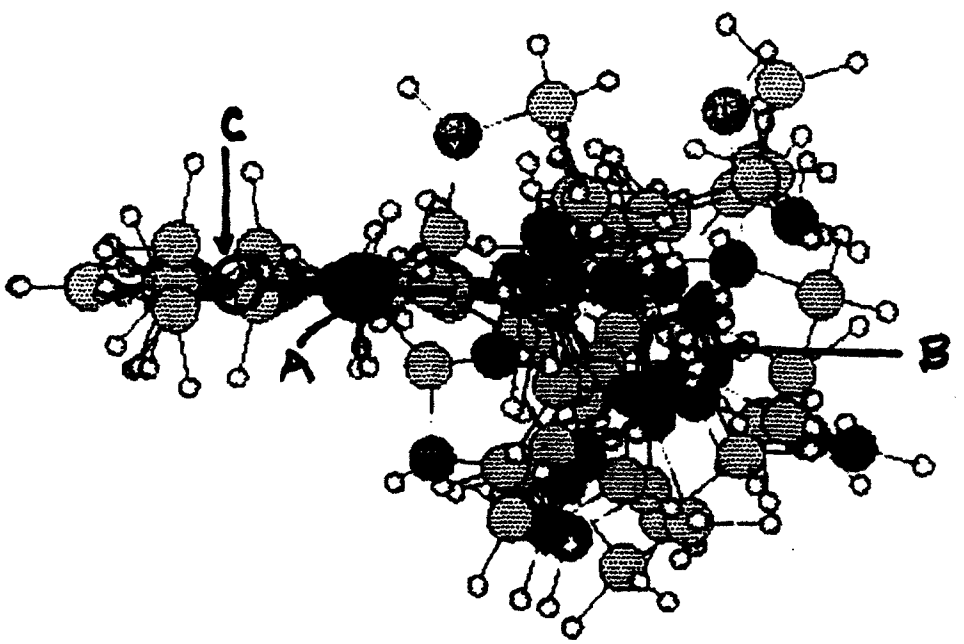
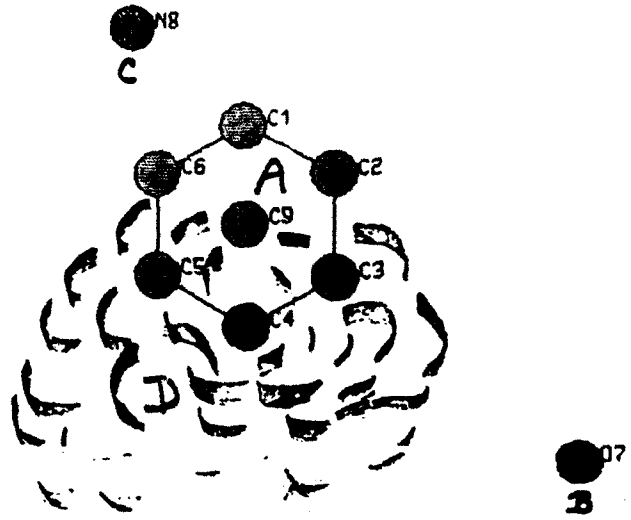


Figure 3. The 14 Alpha2-Adrenergic Agonists Overlap Rotated 90°



C	1	-0.002150	1.356758	0.000408
C	2	1.218220	0.685591	-0.002984
C	3	1.198375	-0.744489	-0.003420
C	4	0.013530	-1.408066	-0.000545
C	5	-1.203950	-0.686029	0.002874
C	6	-1.195631	0.704377	0.003309
O	7	4.439856	-3.321824	-1.243940
N	8	-1.506316	2.716918	-0.671336
C	9	0.000000	0.000000	0.000000

Figure 4. PM3 Alpha2-Adrenoceptor Pharmacophore Interaction Template

Figure 5. PM3 Alpha2-Adrenoceptor Pharmacophore Template Rotated 90°

figures as a cloud that represents an area for lipophilic or hydrophobic binding. This area can accommodate functional groups that are lipophilic (i.e., halides, hydrophobic carbon containing groups).

3.3 Intra-Atomic Distances and Angles.

Figures 6 and 7 illustrate intra-atomic distances that were measured using the MMADS Bond option of the MMADS EDIT routine. The distances were as follows: (a) the distance from the center of the planar ring of the compound to the nitrogen whose proton was predicted to interact with the adrenoceptor (A); (b) the distance from the center of the planar ring to the proton (B); (c) the distance from the plane of the planar ring to the nitrogen (C); and (d) the distance from the ring plane to the proton (D).

Additional compound measurements were made of the angle formed by the center of the planar ring, the above selected nitrogen, and its proton.

The Table gives the measurements for the distances and angles for the 14 compounds.

3.4 Agonist-A2ARPHar Interaction Distance Measurements.

Figure 8 illustrates the distances (E) from the nitrogen of the agonist to the proposed proton binding region of the pharmacophore and (F) from the agonist's proton to this pharmacophore region. The Table lists the measured distances.

3.5 Electronic Charge Measurements.

The Table lists the electronic charge units (PM3 Charge NH+) of each compound for the nitrogen proton environment that is predicted to interact with the A2AR. The unit is calculated by adding the PM3 formal charges of the nitrogen and its bonded hydrogen that the molecular modeling analysis predicted to interact with the A2AR.

4. DISCUSSIONS

4.1 Relationships with Other A2ARPHar Models.

Molecular modeling studies to predict the environment of the A2AR receptor environment are limited to a small number of selective agonist classes (phenethlyamines, clonidine-type imidazoles) or involved antagonists. Reviews by Ruffolo,[6] Savola,[5] and Guptka[19] discuss the various SARs with various classes of alpha2-adrenergic compounds and describe model pharmacophores for compound receptor interactions. This study has evaluated the models of Ruffolo[6], Hancock,[22] Kier,[23] Pullman,[24] Easson-Stedman,[25] and Timmermans.[26]

Table. Distance and Charge Measurements for Alpha2-Adrenergic Agonists

Compound Name	Center to N	Center to H+	Plane to N	Plane to H+	Angle (Center-N-H+)	A2ARPHar to N	A2ARPHar to H+	PM3 Charge (NH+)
	(A)	(B)	(C)	(D)		(E)	(F)	
A62032 (S)	4.73	5.01	0.05	-1.01	98.7	2.483	2.507	0.34
A62033 (R)	4.94	5.39	-0.90	-0.07	111.8	2.769	2.925	0.31
BHT920	4.21	4.80	0.04	-0.66	120.5	2.103	1.327	0.67
BHT933	4.08	4.67	0.03	-0.66	120.8	2.035	1.231	0.67
Clonidine	5.00	5.49	-0.98	-0.11	111.2	1.351	0.965	0.31
Guanabenz	5.16	5.48	0.09	-0.80	103.7	0.872	0.277	0.13
Guanfacine	5.23	5.59	-1.10	-0.81	106.0	1.001	0.283	0.11
M-7	5.19	5.35	0.41	0.68	93.5	2.098	1.523	0.72
Medetomidine	5.12	5.63	-1.40	-0.69	116.8	1.097	0.180	0.56
Moxonidine	5.13	5.55	-1.74	-1.03	114.1	1.448	0.503	0.23
Noradrenaline	5.17	5.58	-1.16	-0.57	110.1	1.307	0.499	0.93
Alphamethyl-Noradrenaline	5.15	5.47	-1.53	-1.28	103.1	1.570	0.809	0.86
UK14304	5.10	5.43	-0.52	-0.50	104.1	1.109	0.156	0.33
YAII085	5.09	5.65	-1.41	-0.66	116.2	1.158	0.250	0.54

NOTES:

Distances are measured in Angstrom units.
The PM3 charge is the electrostatic charge environment measured by adding the formal charge of the compound's nitrogen and hydrogen closest to the predicted adrenoceptor negative region. It is measured in electronic charge units.

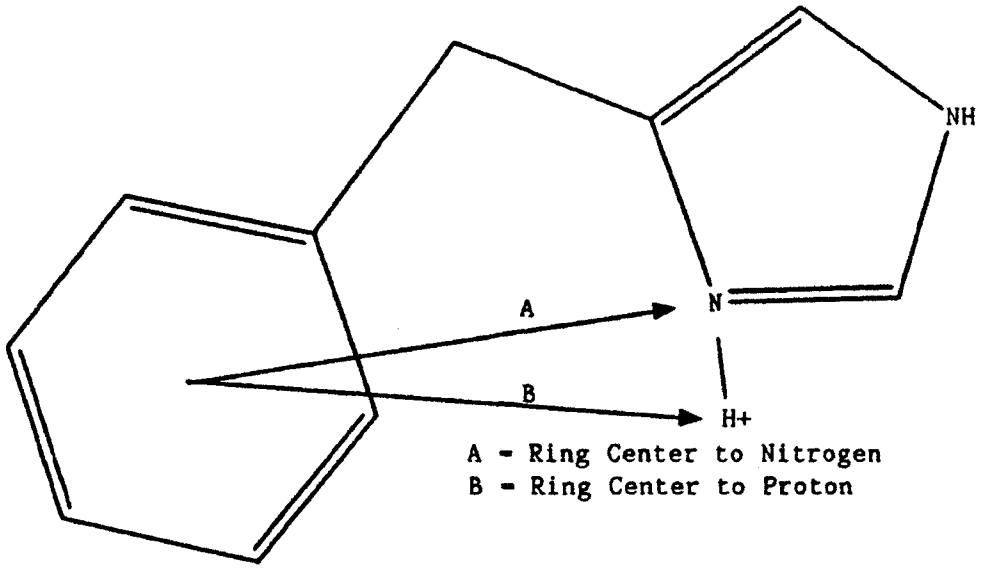


Figure 6. Example of Intra-Atomic Distance Measurements

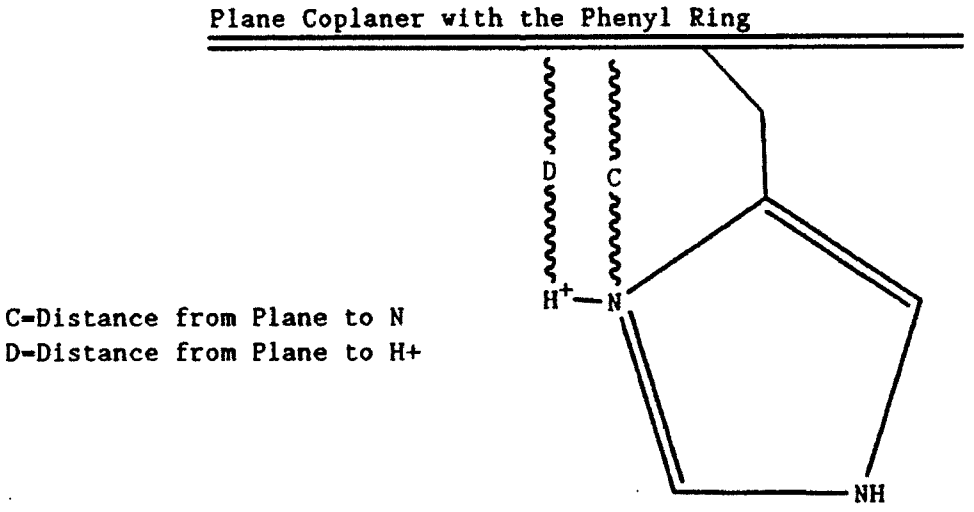


Figure 7. Example of Plane to Nitrogen and Proton Measurements

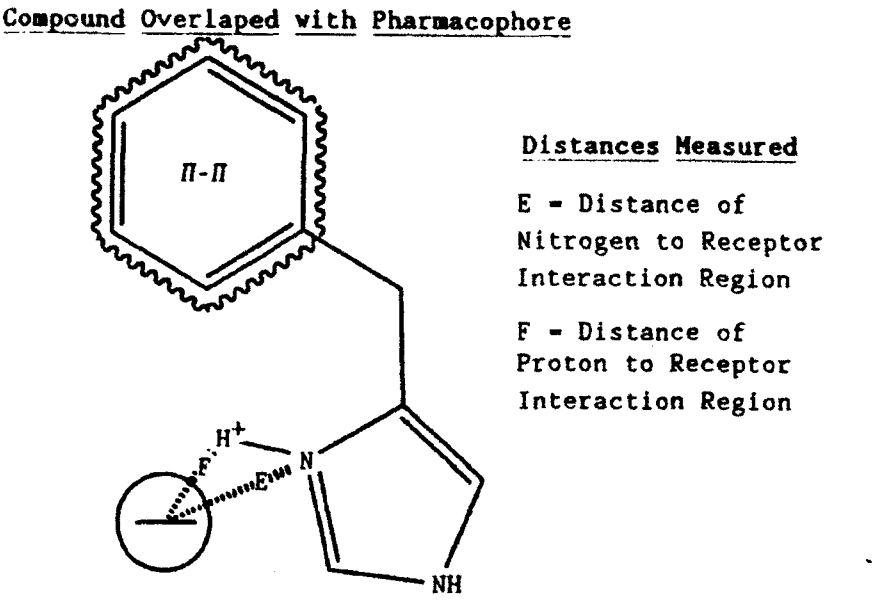


Figure 8. Agonist-Adrenoceptor Pharmacophore Interaction Distance Measurements

An additional model by Lloyd and Andrews[27] defining a common structural model for central nervous system compounds was also evaluated. Our molecular modeling analysis of alpha2-adrenergic agonists supports these findings.

Our A2ARPHar model incorporates many of the same features as previous models; but, our study specifically addresses alpha2-adrenergic agonists and provides additional insight to the importance of the position of the compound's proton in resultant agonist activity. Our model also provides three-dimensional Cartesian coordinates of a proposed A2AR environment that can be used as a compound/receptor interaction template for future structure-activity studies.

The following three compound regions are common to all the proposed models (including our A2ARPHar): (a) a planar ring; (b) a nitrogen environment; and (c) a bridge region that separates the planar ring system from the nitrogen region.

4.2 Planar Ring Region.

Figure 1 illustrates the various planar ring systems (mainly aromatic) that can interact with the A2AR. Figures 2 and 3 illustrate the planarity of the ring systems for the various types of rings and show that the

rings can be overlapped in a common orientation (Region A). This type of compound/receptor interaction could involve charge transfer interactions, ion-induced dipole, or lipophilic binding. The molecular analysis suggests that one may be limited in the position, size, and type of the substituent on the planar ring to maintain agonist activity. Previous studies[5,6,19] described SARs for substituents on the ring systems for a variety of classes of compounds. We propose that in developing SARs for alpha2 agonists that investigators orient the planar ring system as illustrated in our model; the same relationships will generally hold for other planar ring systems. Hancock[22] provides some insight as to the spatial domains necessary to maintain agonist activity. In our study, the agonists studied fit these domains. Two compounds not analyzed in the previous studies, UK14304 and YAII085, extend the domain of the planar ring system. The YAII085 compound was specifically designed to evaluate the spatial domain and lipophilic region of the model. Figures 9 and 10 illustrate the increased spatial domain of the planar region for the interaction of these compounds and for the interaction of clonidine with the A2ARPHar model.

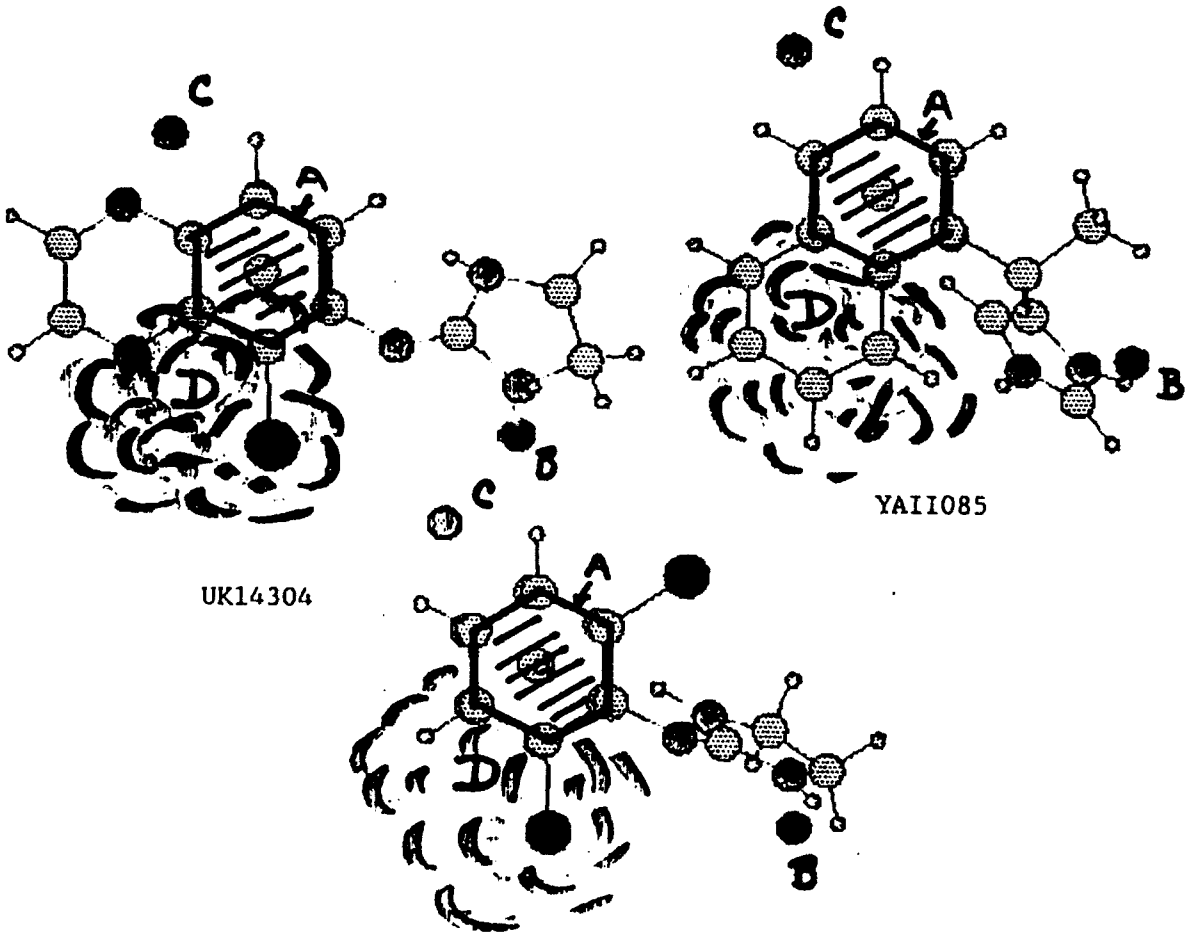


Figure 9. UK14304, YAII085, and Clonidine Interaction with A2ARPHar

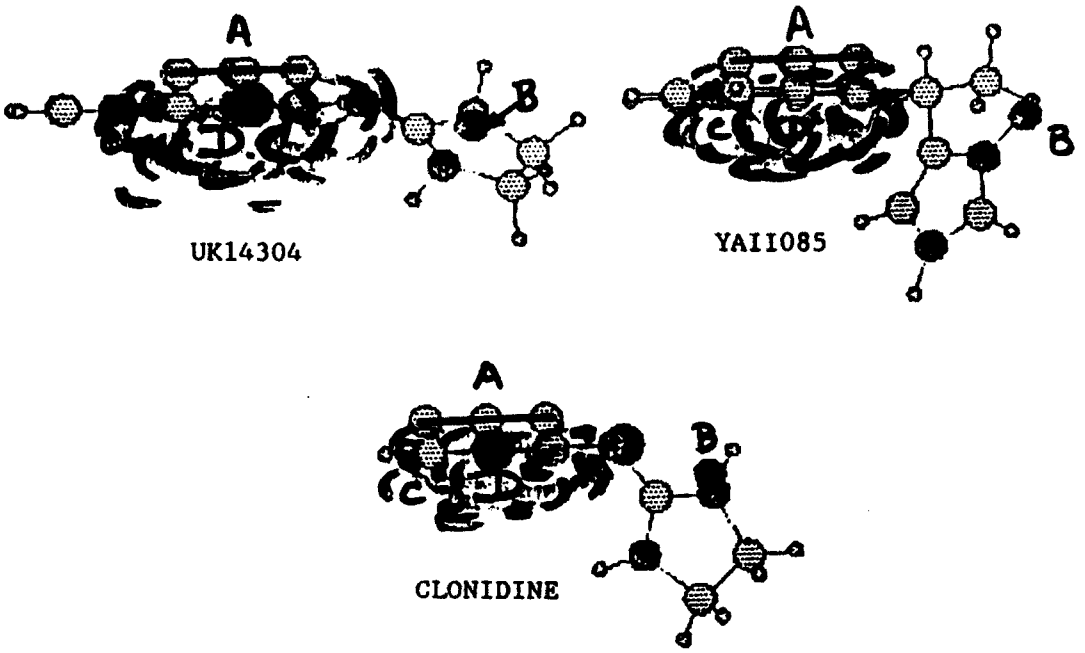


Figure 10. UK14304, YAII085, and Clonidine Interaction with A2ARPHar Rotated 90°

4.3 Nitrogen Environment.

Figure 1 illustrates the alpha2-adrenergic agonists various nitrogen environments. The compound nitrogen environment/receptor interaction may involve ionic, ion-induced dipole, or noncoulombic van der Waals types.

Previous studies[5,6,20,23,24,27] suggest that agonist activity relates to the distance (see Table, Column A) from the center of the planar ring system to the nitrogen is predicted to interact with the receptor. Additionally, the distance (see Table, Column C) from the plane formed by the ring system to the nitrogen was suggested for measurement as a potential for identifying a feature common to alpha2-adrenergic agonists. The Table lists the above measured distances (Columns A and C) for the agonists studied. The center of ring to the nitrogen distance varied from 4.21 Å for BHT920 to 5.31 Å for M-7. The plane to nitrogen distance varied from 0.41 Å for M-7 to -1.75 Å for Moxonidine.

Although all of the compounds are agonists at the A2AR, there are differences in the degree of their action. In analyzing the above measurements for the A2ARPHar model development, the distance variation did not allow for a quantitative positioning of the pharmacophore interaction region (Figures 4 and 5, Region B). Therefore, since these compounds may protonate at physiological pH, the compounds were protonated and another molecular analysis was performed. The analysis identified that the protonated species of the agonists BHT920, BHT933, Medetomidine, Moxonidine, UK14304, and the crystal structures of Noradrenaline and YAII085 had a common plane to H+ distance of -0.66 + 0.1 (-0.56 to -0.76) Å. Important to note is that although the nitrogen for these compounds is located in different

three-dimensional positions, the protons are all positioned so that they lie in the same plane. Additionally, the protons are directed away from the center of the planar ring (indicated by the angle (in the Table, Center-N-H+), which would orient the proton for "best interaction" with the A2AR).

Figures 2, 3, 9, and 10 illustrate the above relationship. The protons are represented as the smallest circles seen near the B region. The figures show the bond between the proton and its nitrogen and the direction of the proton towards Region B.

Because of these observations, additional measurements were made to identify the distances (see Table, Columns E and F) from our proposed A2ARPHar model to the nitrogen of the agonists and the proton to evaluate how the compounds would interact with the A2ARPHar model. In the overlap orientation, the protons of compounds A62032, A62033, BHT920, BHT933, and M-7 are positioned at distances (see Table, Column F) >1.2 Å from the proposed A2ARPHar region. If one overlapped them, as in the original analysis, the compounds would not fit geometrically to interact with Region B of the A2ARPHar model. Investigators would propose that the better the compounds fit (geometrically, physicochemically, and electrostatically) to Regions A and B of the pharmacophore, the more enhanced their activity would be.

Compounds BHT920 and BHT933 are selective alpha2-adrenergic agonists. One can position BHT920 and BHT933 to interact more closely to Region B by simply moving the compounds in the x direction. Their protons are situated at the appropriate ring to planar distance -0.67 Å. Figure 11 illustrates the resultant BHT920/A2ARPHar interaction.

Similarly, a better fit of A62032, A62033, and M-7 can be obtained by rotating each molecule around Region B. Figure 12 illustrates the resultant A62032/A2ARPHar interaction.

4.4 Bridge Area Between the Compound's Planar Ring and Nitrogen Environment.

Ruffolo[6] and Savola[5] describe the various atom types that can be used to separate the planar ring system and the nitrogen of the alpha2-adrenergic agonists. The most important characteristics for resultant activity follow: (1) the ability of the bridge to orient the proton of the compound at the corresponding three-dimensional position for interaction with the A2AR, and (2) the substitution at the bridge regions that may change the formal charge in the nitrogen environment or may sterically hinder the proton from interacting properly with the A2AR.

4.5 A2ARPHar Region C.

Region C of the A2ARPHar is proposed for possible hydrogen bonding interaction for certain alpha2-adrenergic agonists. However, there is not enough data to quantitatively determine if this region exists in all the subtypes of A2ARs; the region may exist in postsynaptic or peripheral A2AR's but not in central or presynaptic A2ARs.

This region in the A2ARPHar model is suggested for future analysis.

4.6 Hydrophobic Cleft or Lipophilic Region.

The proposed A2ARPHar hydrophobic cleft or lipophilic region (Figures 4 and 5) is similar to the proposed lipophilic/aromatic region proposed by Ruffolo.[6] This study that includes Savola's compounds[5] and the YAII085 compound[10] extends the geometric dimensions of this region. Generally, the study extends the dimensions of the planar ring system from a small phenyl type to include a region that can accommodate a naphthalene ring.

4.7 Structure-Activity Relationships.

The proposed A2ARPHar model can be used for in vitro ligand binding and in vivo physiological studies as a "pharmacophore" template for analyzing compounds that act on the A2AR, for better defining the environment of the A2AR, and for use in designing of compounds having desired pharmacological effects. The model can be used to identify compound functional groups in relation to potential interaction areas on the receptor template; thereby, investigators can use more efficient structure-activity methods to analyze congeneric series of alpha2-adrenergic compounds.

We suggest protonating the compound at the nitrogen environment for a proposed interaction with the A2AR. Next, we suggest reconstructing the proposed pharmacophore and initially orienting each compound to be analyzed to the A2RPHar planar ring Region A. Each compound's ring system should be directly overlapped. After overlapping, the pharmacophore should be raised 0.7 Å above the compound's ring as shown in Figures 10 and 11. This repositioning allows for appropriate contact atom bond radii for interaction of the compound with the proposed pharmacophore.

Researchers should then note the position of the proton in relationship to Region B. Positioning of the molecule would then be used as part of the overall structure-activity analysis.

4.8 Drug Design.

The A2ARPHar model can be used in drug design and structure-activity studies in the following ways: (a) to identify parameters of tested compounds for isolation of features related to alpha2-adrenergic activity; (b) to recommend new compounds for experimentation, incorporating structural and physicochemical features suggested by the model; (c) to identify new directions (new lead series of compounds) that may increase drug efficacy or improve the current pharmacophore model; and (d) to aid in an improved understanding of the mechanisms and structural models of the alpha2-adrenergic system as related to the pharmacological action of compounds.

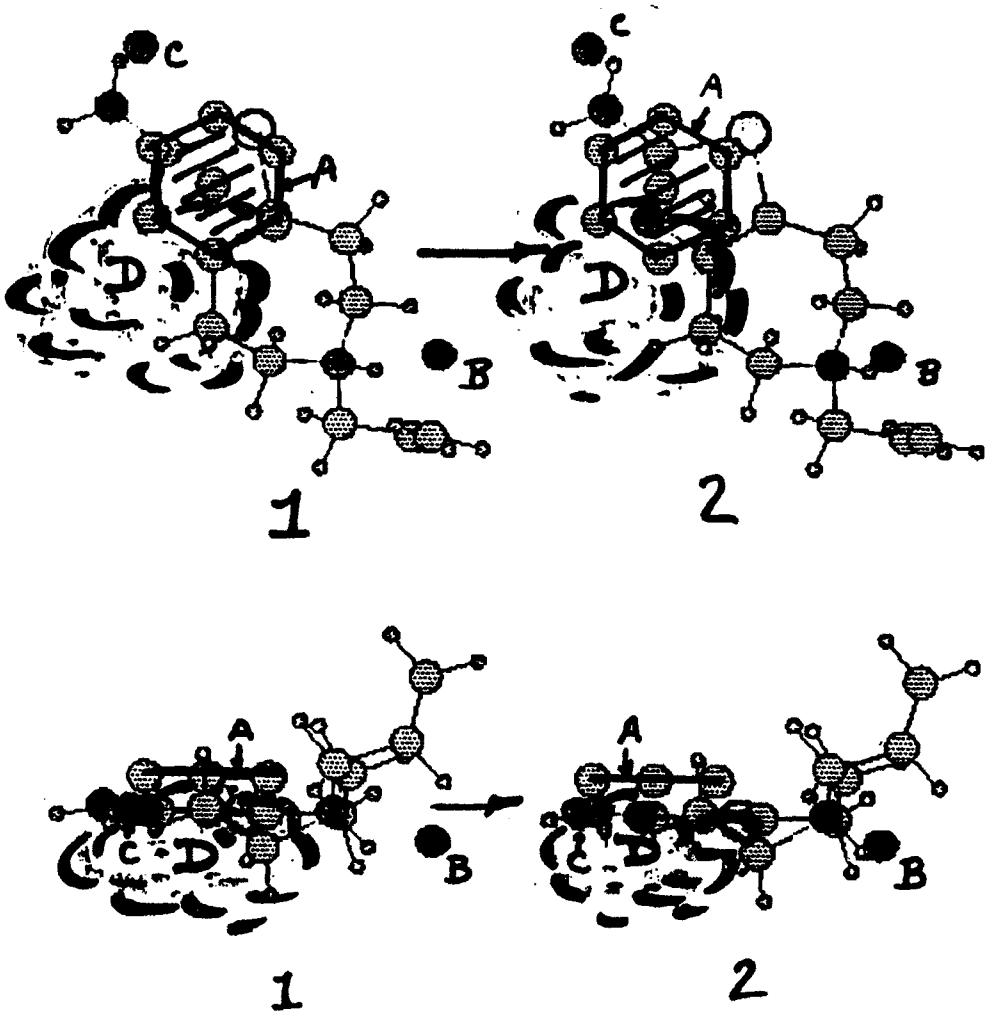


Figure 11. BHT920/A2ARPHar Interactions

1. BHT920 Overlapped on A2ARPHar Region A
2. BHT920 Moved Towards Region B

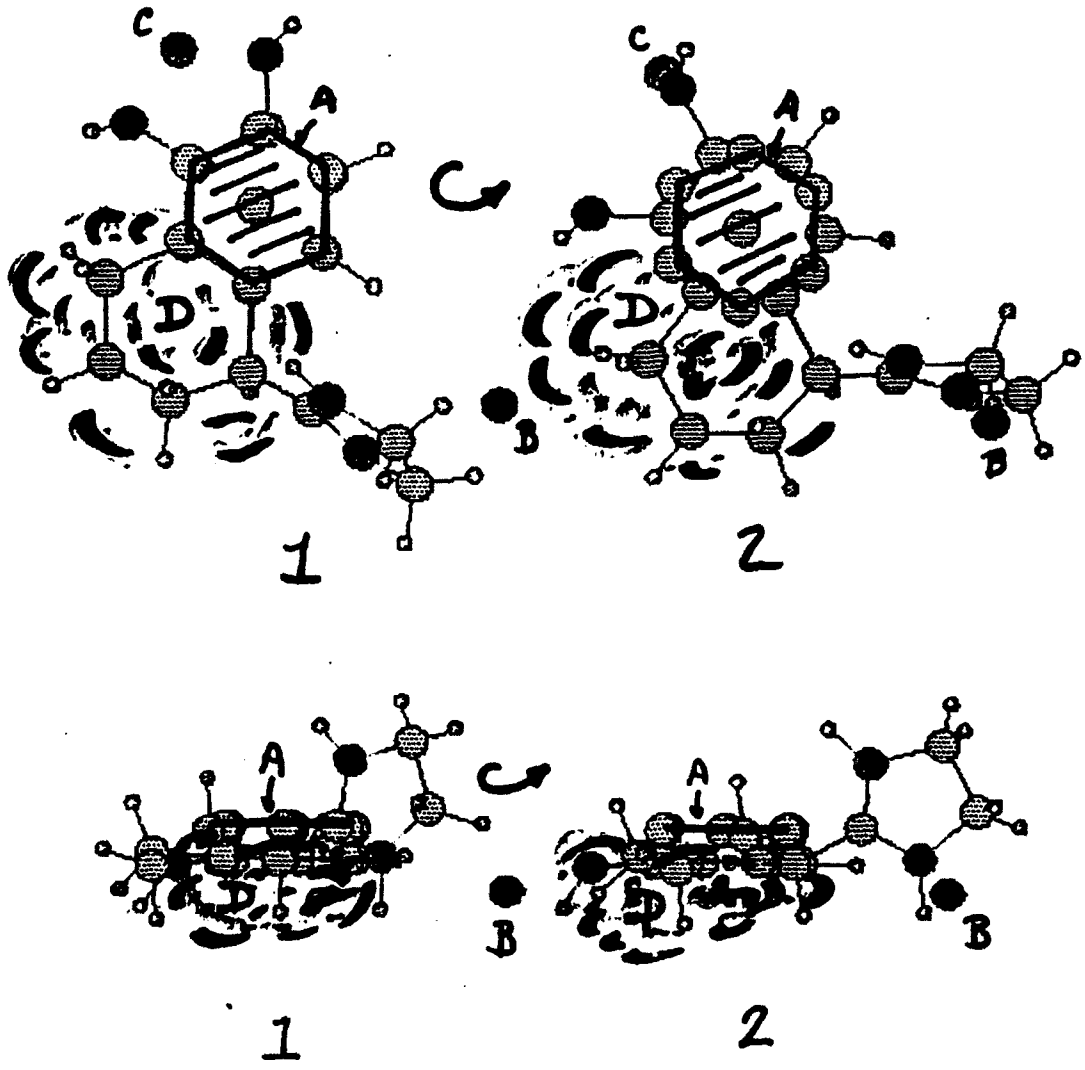


Figure 12. A62032/A2ARPHar Interactions

1. A62032 Overlapped on A2ARPHar Region A
2. A62032 Rotated on Region A

5. CONCLUSIONS

A pharmacophore model of an alpha2-adrenergic receptor agonist environment is defined in relation to the physicochemical and three-dimensional structural features of compounds known to be agonists with the alpha2-adrenoceptor. Also, important to the agonist activity of the compounds is the position of a proton of the compound's protonated form in relation to the center of its planar ring.

The model can be used as a drug-receptor interaction template in structure-activity, biochemical ligand binding, and drug design studies for correlation and/or recommendation of new compounds having improved pharmacological action.

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APPENDIX A
COMPOUND STRUCTURE FILE FORMAT

The compound structure file is the primary data structure of MMADS, containing all of the required molecular information. The data records contained in the chemical compound structure file are listed below.

Record #1 - the header record for the file

Column Nos. 1-3 The number of atoms contained in the file

Column Nos. 4-72 The title of the structure file

Record #2 - The descriptions of the individual atoms

Column No. - 1 Blank

Column Nos. 2-3 The atom symbol

Column Nos. 4-8 The atom index

Column Nos. 9-20 The x-coordinate

Column Nos. 21-32 The y-coordinate

Column Nos. 33-44 The z-coordinate

Column Nos. 45-49 The atom type (defined below)

Column Nos. 50-79 The atom bond connectivity

MMADS uses the atom type to encode information describing each atom's molecular environment. The atom types used by MMADS are defined below:

Atom Type	Atom Type Description
1	Carbon - sp3
2	Carbon - sp2
3	Carbonyl Carbon
4	Carbon - sp
5	Hydrogen
6	Oxygen - sp3
7	Oxygen - sp2
8	Nitrogen - sp3

Atom Type	Atom Type Description
9	Nitrogen - sp2
10	Nitrogen - sp
11	Fluorine
12	Chlorine
13	Bromine
14	Iodine
15-18	Sulfur (in development)
19	Silicon
20	(inactive)
21	Alcoholic Hydrogen (N-H, O-H)
22	Cyclopropane Hydrogen
23	Amine Hydrogen
24	Carboxyl Hydrogen
25	Phosphorus

APPENDIX B
COMPOUND THREE-DIMENSIONAL COORDINATES

A62032 (S) CRYSTAL H18

C	1	-0.142032	-1.005426	-0.485563	1	2	10	14	19	35	0
C	2	-1.474451	-1.551968	0.085989	1	1	3	20	21	0	0
C	3	-2.614692	-0.892071	-0.616703	1	2	4	22	23	0	0
C	4	-2.683625	0.591357	-0.342558	1	3	5	24	25	0	0
C	5	-1.323117	1.260984	-0.424872	2	4	6	10	0	0	0
C	6	-1.231141	2.661258	-0.452624	2	5	7	11	0	0	0
C	7	-0.008813	3.324809	-0.449451	2	6	8	12	0	0	0
C	8	1.123600	2.578927	-0.429900	2	7	9	26	0	0	0
C	9	1.071557	1.201987	-0.455376	2	8	10	27	0	0	0
C	10	-0.143500	0.533147	-0.442824	2	1	5	9	0	0	0
O	11	-2.413177	3.366037	-0.571941	6	6	28	0	0	0	0
O	12	-0.082530	4.679329	-0.473058	6	7	29	0	0	0	0
N	13	1.894428	-2.364099	-0.391689	9	14	17	18	0	0	0
C	14	1.004077	-1.606520	0.223079	2	1	13	15	0	0	0
N	15	1.258124	-1.448641	1.514812	8	14	16	30	0	0	0
C	16	2.486379	-2.155879	1.880076	1	15	17	31	32	0	0
C	17	2.845099	-2.915977	0.561670	1	13	16	33	34	0	0
H	18	1.914114	-2.548556	-1.455639	23	13	0	0	0	0	0
H	19	-0.082709	-1.339945	-1.521266	5	1	0	0	0	0	0
H	20	-1.523861	-2.629545	-0.070496	5	2	0	0	0	0	0
H	21	-1.529468	-1.336358	1.153034	5	2	0	0	0	0	0
H	22	-2.498573	-1.043895	-1.689813	5	3	0	0	0	0	0
H	23	-3.544433	-1.352556	-0.282583	5	3	0	0	0	0	0
H	24	-3.344989	1.052095	-1.076327	5	4	0	0	0	0	0
H	25	-3.088168	0.743501	0.658091	5	4	0	0	0	0	0
H	26	2.083385	3.072794	-0.393719	5	8	0	0	0	0	0
H	27	1.990468	0.635338	-0.485560	5	9	0	0	0	0	0
H	28	-3.043943	3.205294	-1.408539	21	11	0	0	0	0	0
H	29	0.377140	5.248578	0.293924	21	12	0	0	0	0	0
H	30	0.646420	-0.879730	2.199326	23	15	0	0	0	0	0
H	31	3.275082	-1.456934	2.158512	5	16	0	0	0	0	0
H	32	2.310737	-2.851870	2.700347	5	16	0	0	0	0	0
H	33	2.706983	-3.990978	0.677413	5	17	0	0	0	0	0
H	34	3.871455	-2.711749	0.256738	5	17	0	0	0	0	0

A62033 PROTONATED H29

C	1	0.095820	-0.957101	0.664294	1	2	10	13	25	0	0
C	2	-1.225130	-1.718079	0.483396	1	1	3	14	15	0	0
C	3	-2.352289	-1.012366	1.211594	1	2	4	16	17	0	0
C	4	-2.550280	0.377394	0.636813	1	3	5	18	19	0	0
C	5	-1.284238	1.171352	0.637779	2	4	6	10	0	0	0
C	6	-1.338986	2.575383	0.660659	2	5	7	11	0	0	0
C	7	-0.148409	3.340489	0.631343	2	6	8	12	0	0	0
C	8	1.093052	2.688802	0.639320	2	7	9	20	0	0	0
C	9	1.136797	1.304589	0.653989	2	8	10	21	0	0	0
C	10	-0.033604	0.540488	0.621928	2	1	5	9	0	0	0
O	11	-2.508086	3.289346	0.695560	6	6	22	0	0	0	0
O	12	-0.096442	4.697387	0.597333	6	7	23	0	0	0	0
H	13	0.520794	-1.213706	1.669853	5	1	0	0	0	0	0
H	14	-1.484958	-1.814685	-0.589920	5	2	0	0	0	0	0
H	15	-1.113832	-2.752814	0.862096	5	2	0	0	0	0	0
H	16	-3.287909	-1.598750	1.119453	5	3	0	0	0	0	0
H	17	-2.133939	-0.959453	2.297360	5	3	0	0	0	0	0
H	18	-2.927299	0.313544	-0.404764	5	4	0	0	0	0	0
H	19	-3.340242	0.914922	1.208751	5	4	0	0	0	0	0
H	20	2.021036	3.274508	0.650057	5	8	0	0	0	0	0
H	21	2.114031	0.810544	0.710694	5	9	0	0	0	0	0
H	22	-3.214995	2.684407	0.911166	21	11	0	0	0	0	0
H	23	-0.977873	5.050347	0.620414	21	12	0	0	0	0	0
N	24	1.088233	-0.953881	-1.685144	8	25	28	34	0	0	0
C	25	1.052399	-1.419788	-0.408096	2	1	24	26	0	0	0
N	26	1.996011	-2.390540	-0.260052	8	25	27	29	0	0	0
C	27	2.789187	-2.602435	-1.509821	1	26	28	30	31	0	0
C	28	2.179231	-1.587740	-2.487078	1	24	27	32	33	0	0
H	29	2.149399	-2.905238	0.574822	23	26	0	0	0	0	0
H	30	3.867960	-2.428438	-1.316440	5	27	0	0	0	0	0
H	31	2.696900	-3.651934	-1.857267	5	27	0	0	0	0	0
H	32	1.758739	-2.057811	-3.399386	5	28	0	0	0	0	0
H	33	2.907753	-0.826697	-2.833230	5	28	0	0	0	0	0
H	34	0.551172	-0.182045	-2.007481	23	24	0	0	0	0	0

BHT920 PROTONATED H30

S	1	-0.771936	3.560297	-0.511761	15	2	5	0	0	0	0
C	2	-2.486437	3.118230	-0.481858	2	1	3	13	0	0	0
N	3	-2.700613	1.783118	-0.458927	9	2	4	0	0	0	0
C	4	-1.493360	1.072516	-0.450361	2	3	5	12	0	0	0
C	5	-0.366011	1.863278	-0.483076	2	1	4	11	0	0	0
C	6	-0.437676	-1.079665	-1.174430	1	7	12	14	15	0	0
N	7	0.896790	-1.136522	-0.434753	8	6	8	9	30	0	0
C	8	1.238634	0.136700	0.330822	1	7	11	16	17	0	0
C	9	0.947689	-2.345359	0.503393	1	7	10	18	19	0	0
C	10	2.345279	-2.606509	0.946296	2	9	20	21	0	0	0
C	11	1.041835	1.405349	-0.492603	1	5	8	23	24	0	0
C	12	-1.565307	-0.413771	-0.397534	1	4	6	25	26	0	0
N	13	-3.563597	3.986429	-0.362282	8	2	27	28	0	0	0
H	14	-0.286270	-0.540191	-2.137373	5	6	0	0	0	0	0
H	15	-0.730191	-2.118186	-1.450305	5	6	0	0	0	0	0
H	16	0.624780	0.189844	1.259087	5	8	0	0	0	0	0
H	17	2.295006	0.049801	0.671923	5	8	0	0	0	0	0
H	18	0.258183	-2.175303	1.361707	5	9	0	0	0	0	0
H	19	0.558858	-3.243564	-0.028468	5	9	0	0	0	0	0
C	20	2.699816	-2.606199	2.228028	2	10	22	29	0	0	0
H	21	3.064564	-2.880426	0.161655	5	10	0	0	0	0	0
H	22	2.016866	-2.379441	3.045028	5	20	0	0	0	0	0
H	23	1.396007	1.272860	-1.537866	5	11	0	0	0	0	0
H	24	1.690491	2.197458	-0.061382	5	11	0	0	0	0	0
H	25	-1.594406	-0.748087	0.662028	5	12	0	0	0	0	0
H	26	-2.529175	-0.754936	-0.836158	5	12	0	0	0	0	0
H	27	-4.458656	3.605021	-0.559130	23	13	0	0	0	0	0
H	28	-3.409694	4.896589	-0.723214	23	13	0	0	0	0	0
H	29	3.711494	-2.846322	2.548246	5	20	0	0	0	0	0
H	30	1.607037	-1.263010	-1.136732	23	7	0	0	0	0	0

BHT933 PROTONATED H29

O	1	-0.445639	2.442667	-0.211817	6	2	5	0	0	0	0
C	2	-1.826241	2.366191	-0.205258	2	1	3	13	0	0	0
N	3	-2.249347	1.084846	-0.194259	9	2	4	0	0	0	0
C	4	-1.089523	0.283622	-0.186254	2	3	5	12	0	0	0
C	5	-0.000493	1.122623	-0.198819	2	1	4	11	0	0	0
C	6	0.083529	-1.758363	-0.935373	1	7	12	14	15	0	0
N	7	1.408967	-1.737622	-0.168576	8	6	8	9	29	0	0
C	8	1.690008	-0.458054	0.616032	1	7	11	16	17	0	0
C	9	1.489906	-2.955791	0.754219	1	7	10	18	19	0	0
C	10	2.874330	-3.180030	1.324842	1	9	20	21	28	0	0
C	11	1.445910	0.829624	-0.169214	1	5	8	22	23	0	0
C	12	-1.114657	-1.194539	-0.176016	1	4	6	24	25	0	0
N	13	-2.565779	3.541778	-0.077151	8	2	26	27	0	0	0
H	14	0.218248	-1.187882	-1.883300	5	6	0	0	0	0	0
H	15	-0.124542	-2.809875	-1.239118	5	6	0	0	0	0	0
H	16	1.069368	-0.455966	1.541951	5	8	0	0	0	0	0
H	17	2.749331	-0.495779	0.960163	5	8	0	0	0	0	0
H	18	0.742478	-2.838935	1.570898	5	9	0	0	0	0	0
H	19	1.168421	-3.854157	0.178808	5	9	0	0	0	0	0
H	20	2.896472	-4.138430	1.865082	5	10	0	0	0	0	0
H	21	3.169178	-2.404943	2.048263	5	10	0	0	0	0	0
H	22	1.855832	0.772795	-1.199515	5	11	0	0	0	0	0
H	23	1.998420	1.656520	0.325539	5	11	0	0	0	0	0
H	24	-1.162863	-1.570145	0.868499	5	12	0	0	0	0	0
H	25	-2.044726	-1.559467	-0.662734	5	12	0	0	0	0	0
H	26	-3.523599	3.424987	-0.312549	23	13	0	0	0	0	0
H	27	-2.140103	4.336607	-0.492187	23	13	0	0	0	0	0
H	28	3.652651	-3.235304	0.549506	5	10	0	0	0	0	0
H	29	2.137625	-1.824352	-0.857453	23	7	0	0	0	0	0

CLONIDINE CRYSTAL H16

CL	1	0.595701	2.416811	1.109814	12	7	0	0	0	0	0
CL	2	-2.022835	-2.298600	1.073673	12	11	0	0	0	0	0
N	3	0.411976	-0.587613	1.103078	9	6	12	0	0	0	0
N	4	0.945424	-0.211651	-1.156714	8	12	13	15	0	0	0
N	5	2.367600	-1.325500	0.077219	8	12	14	16	0	0	0
C	6	-0.823729	0.107530	1.072460	2	3	7	11	0	0	0
C	7	-0.872814	1.497719	1.078640	2	1	6	8	0	0	0
C	8	-2.076544	2.176974	1.068875	2	7	9	17	0	0	0
C	9	-3.260002	1.472635	1.052359	2	8	10	18	0	0	0
C	10	-3.246675	0.101555	1.058996	2	9	11	19	0	0	0
C	11	-2.037475	-0.574622	1.068978	2	2	6	10	0	0	0
C	12	1.199987	-0.709344	0.041262	2	3	4	5	0	0	0
C	13	2.038737	-0.489095	-2.068505	1	4	14	20	21	0	0
C	14	3.041583	-1.258321	-1.201621	1	5	13	22	23	0	0
H	15	0.047276	0.327187	-1.420122	23	4	0	0	0	0	0
H	16	2.768847	-1.817490	0.950916	23	5	0	0	0	0	0
H	17	-2.089061	3.256888	1.074181	5	8	0	0	0	0	0
H	18	-4.201286	2.001832	1.034124	5	9	0	0	0	0	0
H	19	-4.175579	-0.449382	1.056452	5	10	0	0	0	0	0
H	20	1.701371	-1.098170	-2.907141	5	13	0	0	0	0	0
H	21	2.477185	0.435658	-2.443597	5	13	0	0	0	0	0
H	22	3.985780	-0.719760	-1.120735	5	14	0	0	0	0	0
H	23	3.224532	-2.255242	-1.602594	5	14	0	0	0	0	0

GUANABENZ PROTONATED H21

N	1	1.734694	-2.125162	-0.282222	8	2	5	21	23	0	0
C	2	2.699888	-1.736751	0.826677	2	1	3	15	0	0	0
N	3	2.557563	-2.373870	1.927675	9	2	4	0	0	0	0
H	4	3.119972	-2.204319	2.719362	23	3	0	0	0	0	0
N	5	0.460777	-1.414577	-0.287872	9	1	12	0	0	0	0
C	6	-0.921901	0.544477	-0.373275	2	7	11	12	0	0	0
C	7	-2.156468	-0.134990	-0.375234	2	6	8	18	0	0	0
C	8	-3.360981	0.577995	-0.376407	2	7	9	19	0	0	0
C	9	-3.359977	1.963782	-0.373947	2	8	10	20	0	0	0
C	10	-2.148863	2.658484	-0.376747	2	9	11	13	0	0	0
C	11	-0.950927	1.961252	-0.381597	2	6	10	14	0	0	0
C	12	0.365606	-0.106124	-0.355651	2	5	6	22	0	0	0
H	13	-2.142029	3.756508	-0.375448	5	10	0	0	0	0	0
CL	14	0.473725	2.860514	-0.388912	12	11	0	0	0	0	0
N	15	3.576444	-0.642659	0.451200	8	2	16	17	0	0	0
H	16	4.411365	-0.994342	0.032225	5	15	0	0	0	0	0
H	17	3.783584	-0.063560	1.235359	5	15	0	0	0	0	0
CL	18	-2.264555	-1.797900	-0.374378	12	7	0	0	0	0	0
H	19	-4.309749	0.024726	-0.376743	5	8	0	0	0	0	0
H	20	-4.307574	2.517039	-0.371438	5	9	0	0	0	0	0
H	21	2.180727	-1.999456	-1.171558	23	1	0	0	0	0	0
H	22	1.260575	0.549418	-0.396652	5	12	0	0	0	0	0
H	23	1.447957	-3.082319	-0.178216	23	1	0	0	0	0	0

GUANFACINE PROTONATED H25

N	1	1.831767	-1.416907	-0.462561	9	2	5	21	0	0	0
C	2	2.988440	-1.096314	-1.175990	2	1	3	15	0	0	0
N	3	3.301145	0.232540	-1.396034	8	2	4	25	0	0	0
H	4	3.989292	0.452147	-2.079639	23	3	0	0	0	0	0
C	5	0.576510	-0.584940	-0.507807	2	1	12	24	0	0	0
C	6	-1.359530	0.338237	0.818402	2	7	11	12	0	0	0
C	7	-1.371655	1.738128	0.820145	2	6	8	18	0	0	0
C	8	-2.566200	2.452449	0.869047	2	7	9	19	0	0	0
C	9	-3.776356	1.767760	0.926803	2	8	10	20	0	0	0
C	10	-3.790605	0.377293	0.919220	2	9	11	13	0	0	0
C	11	-2.589457	-0.328200	0.867166	2	6	10	14	0	0	0
C	12	-0.074282	-0.417610	0.843859	1	5	6	22	23	0	0
H	13	-4.741983	-0.169402	0.952588	5	10	0	0	0	0	0
CL	14	-2.652363	-2.014873	0.880654	12	11	0	0	0	0	0
N	15	3.875395	-2.076249	-1.576897	8	2	16	17	0	0	0
H	16	4.790537	-1.814464	-1.865668	23	15	0	0	0	0	0
H	17	3.765859	-2.999985	-1.231375	23	15	0	0	0	0	0
CL	18	0.081402	2.600070	0.787098	12	7	0	0	0	0	0
H	19	-2.549103	3.549567	0.860617	5	8	0	0	0	0	0
H	20	-4.720430	2.323418	0.980631	5	9	0	0	0	0	0
H	21	1.716821	-2.365154	-0.164779	23	1	0	0	0	0	0
H	22	-0.233592	-1.418615	1.303861	5	12	0	0	0	0	0
H	23	0.645770	0.114447	1.506934	5	12	0	0	0	0	0
O	24	0.287656	-0.145543	-1.588990	7	5	0	0	0	0	0
H	25	2.574960	0.902200	-1.287282	23	3	0	0	0	0	0

APPENDIX B

M7 PROTONATED H33

C	1	0.472399	-1.312329	-0.349808	1	2	10	25	0	0	0
C	2	1.655398	-0.509704	0.205460	1	1	3	14	15	0	0
C	3	1.736834	0.830777	-0.529206	1	2	4	16	17	0	0
C	4	0.507661	1.652668	-0.175156	1	3	5	18	19	0	0
C	5	-0.769507	0.884443	-0.267056	2	4	6	10	0	0	0
C	6	-1.988437	1.582508	-0.292535	2	5	7	11	0	0	0
C	7	-3.215649	0.878883	-0.292147	2	6	8	12	0	0	0
C	8	-3.209618	-0.522388	-0.287849	2	7	9	20	0	0	0
C	9	-2.001959	-1.204421	-0.295160	2	8	10	21	0	0	0
C	10	-0.788507	-0.514855	-0.290461	2	1	5	9	0	0	0
O	11	-2.066460	2.953097	-0.271980	6	6	22	0	0	0	0
O	12	-4.442914	1.464161	-0.289634	6	7	23	0	0	0	0
H	13	0.656834	-1.601108	-1.407949	5	1	0	0	0	0	0
H	14	1.470959	-0.306044	1.296510	5	2	0	0	0	0	0
N	15	2.950877	-1.341963	0.125080	8	2	24	26	33	0	0
H	16	2.652188	1.392064	-0.251341	5	3	0	0	0	0	0
H	17	1.787430	0.676975	-1.627377	5	3	0	0	0	0	0
H	18	0.603915	2.048290	0.858920	5	4	0	0	0	0	0
H	19	0.452466	2.549848	-0.832441	5	4	0	0	0	0	0
H	20	-4.158286	-1.074424	-0.283202	5	8	0	0	0	0	0
H	21	-2.007977	-2.300802	-0.307235	5	9	0	0	0	0	0
H	22	-1.250596	3.286903	-0.631707	5	11	0	0	0	0	0
H	23	-4.344133	2.408349	-0.301227	5	12	0	0	0	0	0
C	24	3.211610	-2.076224	1.417848	1	15	27	28	29	0	0
H	25	0.338357	-2.258685	0.216092	5	1	0	0	0	0	0
C	26	4.154997	-0.529781	-0.277858	1	15	30	31	32	0	0
H	27	2.390718	-2.774206	1.658332	5	24	0	0	0	0	0
H	28	4.142723	-2.664935	1.360388	5	24	0	0	0	0	0
H	29	3.310842	-1.377629	2.264772	5	24	0	0	0	0	0
H	30	5.020922	-1.177158	-0.495805	5	26	0	0	0	0	0
H	31	3.943748	0.069144	-1.181229	5	26	0	0	0	0	0
H	32	4.456419	0.170573	0.519485	5	26	0	0	0	0	0
H	33	2.801719	-2.032446	-0.592406	5	15	0	0	0	0	0

MEDETOMIDINE PROTONATED H32

N	1	2.752482	-1.464196	-0.950753	9	2	5	32	0	0	0
C	2	2.716112	-1.963631	-2.233147	2	1	3	16	0	0	0
N	3	1.677558	-1.325467	-2.868110	8	2	4	17	0	0	0
C	4	1.061261	-0.429442	-1.990767	2	3	5	18	0	0	0
C	5	1.736086	-0.510908	-0.777470	2	1	4	12	0	0	0
C	6	0.134413	0.892644	0.490111	2	7	11	12	0	0	0
C	7	0.090553	2.290697	0.492602	2	6	8	19	0	0	0
C	8	-1.121307	2.964837	0.517983	2	7	9	20	0	0	0
C	9	-2.307666	2.243931	0.538268	2	8	10	21	0	0	0
C	10	-2.286757	0.848701	0.538772	2	9	11	13	0	0	0
C	11	-1.061154	0.157920	0.520876	2	6	10	14	0	0	0
C	12	1.516822	0.289608	0.466732	1	5	6	15	22	0	0
C	13	-3.585493	0.122724	0.546240	1	10	23	24	28	0	0
C	14	-1.080230	-1.330234	0.516707	1	11	29	30	31	0	0
H	15	2.250543	1.140518	0.391283	5	12	0	0	0	0	0
H	16	3.388443	-2.724126	-2.663607	5	2	0	0	0	0	0
H	17	1.408948	-1.481620	-3.807032	23	3	0	0	0	0	0
H	18	0.196766	0.202597	-2.236701	5	4	0	0	0	0	0
H	19	1.027991	2.862352	0.482992	5	7	0	0	0	0	0
H	20	-1.141076	4.060367	0.525691	5	8	0	0	0	0	0
H	21	-3.268713	2.773468	0.560219	5	9	0	0	0	0	0
C	22	1.835231	-0.471533	1.745904	1	12	25	26	27	0	0
H	23	-3.894349	-0.118064	-0.480043	5	13	0	0	0	0	0
H	24	-3.515777	-0.827983	1.099891	5	13	0	0	0	0	0
H	25	1.241528	-1.393277	1.851005	5	22	0	0	0	0	0
H	26	2.897607	-0.742656	1.816653	5	22	0	0	0	0	0
H	27	1.606715	0.155132	2.619367	5	22	0	0	0	0	0
H	28	-4.387327	0.716794	1.003334	5	13	0	0	0	0	0
H	29	-0.208386	-1.770353	1.024856	5	14	0	0	0	0	0
H	30	-1.981440	-1.719178	1.021832	5	14	0	0	0	0	0
H	31	-1.094521	-1.709497	-0.514896	5	14	0	0	0	0	0
H	32	3.395135	-1.740127	-0.248792	23	1	0	0	0	0	0

MONOXIDINE PROTONATED H29

N	1	0.978692	-0.457326	-1.606460	8	2	5	20	0	0	0
C	2	1.765794	-0.992432	-2.760292	1	1	3	15	21	0	0
C	3	2.636989	-2.087721	-2.135051	1	2	4	14	16	0	0
N	4	2.129820	-2.200966	-0.731446	9	3	5	29	0	0	0
C	5	1.210865	-1.189780	-0.463233	2	1	4	12	0	0	0
C	6	-0.544019	-0.176548	0.900774	2	7	11	12	0	0	0
C	7	-0.603557	1.230201	1.011474	2	6	8	18	0	0	0
N	8	-1.795700	1.885789	1.036633	9	7	9	0	0	0	0
C	9	-2.956415	1.181486	1.012551	2	8	10	19	0	0	0
N	10	-2.949522	-0.193735	1.020897	9	9	11	0	0	0	0
C	11	-1.785070	-0.858292	0.974547	2	6	10	13	0	0	0
N	12	0.691685	-0.913806	0.796756	8	5	6	17	0	0	0
CL	13	-1.844119	-2.541472	1.003705	12	11	0	0	0	0	0
H	14	2.523419	-3.070342	-2.633210	5	3	0	0	0	0	0
H	15	1.097260	-1.375677	-3.557242	5	2	0	0	0	0	0
H	16	3.718945	-1.842340	-2.162641	5	3	0	0	0	0	0
H	17	0.823040	-1.612987	1.493853	23	12	0	0	0	0	0
O	18	0.369454	2.172502	1.003988	6	7	22	0	0	0	0
C	19	-4.254608	1.905980	0.965849	1	9	26	27	28	0	0
H	20	0.168528	0.102948	-1.740385	23	1	0	0	0	0	0
H	21	2.357027	-0.170763	-3.211085	5	2	0	0	0	0	0
C	22	1.602087	1.894011	1.632093	1	18	23	24	25	0	0
H	23	2.263911	1.326859	0.970202	5	22	0	0	0	0	0
H	24	2.005641	2.899097	1.790476	5	22	0	0	0	0	0
H	25	1.493773	1.375058	2.591120	5	22	0	0	0	0	0
H	26	-4.598654	1.988259	-0.077242	5	19	0	0	0	0	0
H	27	-5.039764	1.380875	1.527544	5	19	0	0	0	0	0
H	28	-4.174449	2.926979	1.366253	5	19	0	0	0	0	0
H	29	2.708948	-2.585853	-0.020427	23	4	0	0	0	0	0

NORADRENALINE CRYSTAL H20

O	1	-1.556645	3.283256	0.484788	6	7	24	0	0	0	0
O	2	-3.856775	1.852183	0.394091	6	8	22	0	0	0	0
O	3	1.049784	-2.101869	0.955452	6	11	23	0	0	0	0
N	4	3.194083	-1.439923	-0.881962	8	12	19	20	21	0	0
C	5	-0.217784	-0.131209	0.243759	2	6	10	11	0	0	0
C	6	-0.261968	1.255709	0.296082	2	5	7	13	0	0	0
C	7	-1.472195	1.955318	0.344277	2	1	6	8	0	0	0
C	8	-2.654044	1.196583	0.325635	2	2	7	9	0	0	0
C	9	-2.621796	-0.181226	0.256496	2	8	10	14	0	0	0
C	10	-1.401362	-0.849680	0.211113	2	5	9	15	0	0	0
C	11	1.133541	-0.824221	0.328497	1	3	5	12	16	0	0
C	12	1.760458	-1.042034	-1.028392	1	4	11	17	18	0	0
H	13	0.532769	1.732118	0.314919	5	6	0	0	0	0	0
H	14	-3.484478	-0.676871	0.275886	5	9	0	0	0	0	0
H	15	-1.399815	-1.763791	0.172063	5	10	0	0	0	0	0
H	16	1.768858	-0.162243	0.884294	5	11	0	0	0	0	0
H	17	1.731018	-0.213944	-1.546460	5	12	0	0	0	0	0
H	18	1.292213	-1.777873	-1.499856	5	12	0	0	0	0	0
H	19	3.585935	-1.696474	-1.679235	23	4	0	0	0	0	0
H	20	3.400854	-2.171023	-0.286771	23	4	0	0	0	0	0
H	21	3.727124	-0.745935	-0.499203	23	4	0	0	0	0	0
H	22	-3.695240	2.568895	0.401207	5	2	0	0	0	0	0
H	23	0.851628	-1.981207	1.885956	5	3	0	0	0	0	0
H	24	-1.406161	3.915458	-0.352634	21	1	0	0	0	0	0

ALPHAMETHYLNORADRENALINE PROTONATED H2O

O	1	-1.403905	3.582762	0.666299	6	7	23	0	0	0	0
O	2	-3.821305	2.152607	0.664143	6	8	21	0	0	0	0
O	3	1.047620	-1.987635	1.128556	6	11	22	0	0	0	0
N	4	2.971321	-1.438052	-0.852178	8	12	19	20	27	0	0
C	5	-0.215403	0.089208	0.659460	2	6	10	11	0	0	0
C	6	-0.173432	1.485619	0.685454	2	5	7	13	0	0	0
C	7	-1.363799	2.212949	0.694426	2	1	6	8	0	0	0
C	8	-2.611317	1.538620	0.679979	2	2	7	9	0	0	0
C	9	-2.635624	0.137190	0.672392	2	8	10	14	0	0	0
C	10	-1.443125	-0.572477	0.662477	2	5	9	15	0	0	0
C	11	1.080917	-0.672820	0.638095	1	3	5	12	16	0	0
C	12	1.639612	-0.703108	-0.831213	1	4	11	17	18	0	0
H	13	0.791934	2.006695	0.708793	5	6	0	0	0	0	0
H	14	-3.595803	-0.394530	0.676154	5	9	0	0	0	0	0
H	15	-1.473783	-1.672300	0.671105	5	10	0	0	0	0	0
H	16	1.828248	-0.166805	1.299583	5	11	0	0	0	0	0
H	17	1.804804	0.366080	-1.136219	5	12	0	0	0	0	0
C	18	0.685647	-1.351199	-1.820714	1	12	24	25	26	0	0
H	19	3.362165	-1.396298	-1.772586	23	4	0	0	0	0	0
H	20	3.601632	-1.013101	-0.200737	23	4	0	0	0	0	0
H	21	-3.701157	3.092810	0.719272	21	2	0	0	0	0	0
H	22	0.138499	-2.272985	1.189879	21	3	0	0	0	0	0
H	23	-0.590230	3.906434	1.031840	21	1	0	0	0	0	0
H	24	1.017115	-1.228139	-2.861611	5	18	0	0	0	0	0
H	25	0.534090	-2.424669	-1.631165	5	18	0	0	0	0	0
H	26	-0.306634	-0.876990	-1.741156	5	18	0	0	0	0	0
H	27	2.831914	-2.399865	-0.600330	23	4	0	0	0	0	0

UK14304 PROTONATED H28

BR	1	-1.474809	-2.634306	0.503389	13	7	0	0	0	0	0
H	2	0.549195	1.922485	0.478493	5	11	0	0	0	0	0
N	3	0.822542	-0.846236	0.499476	9	6	12	0	0	0	0
N	4	2.478748	0.464190	-0.841978	8	12	13	19	0	0	0
N	5	3.042823	-1.647929	0.200120	8	12	14	23	28	0	0
C	6	-0.360104	-0.071134	0.460344	2	3	7	11	0	0	0
C	7	-1.540915	-0.780725	0.488051	2	1	6	8	0	0	0
C	8	-2.783637	-0.130854	0.489002	2	7	9	15	0	0	0
C	9	-2.805761	1.283123	0.493522	2	8	10	20	0	0	0
C	10	-1.588199	2.014400	0.493173	2	9	11	16	0	0	0
C	11	-0.386368	1.350390	0.468438	2	2	6	10	0	0	0
C	12	1.954831	-0.632667	-0.072690	2	3	4	5	0	0	0
C	13	3.854859	0.122614	-1.299065	1	4	14	17	21	0	0
C	14	4.243020	-1.199666	-0.622024	1	5	13	18	22	0	0
N	15	-3.973642	-0.859693	0.488267	9	8	24	0	0	0	0
H	16	-1.619102	3.112758	0.515210	5	10	0	0	0	0	0
H	17	3.940864	0.057513	-2.403610	5	13	0	0	0	0	0
H	18	5.141553	-1.074791	0.020443	5	14	0	0	0	0	0
H	19	1.861496	0.796604	-1.551002	23	4	0	0	0	0	0
N	20	-4.032521	1.951199	0.494119	9	9	25	0	0	0	0
H	21	4.520261	0.954439	-0.988085	5	13	0	0	0	0	0
H	22	4.521940	-1.973359	-1.371715	5	14	0	0	0	0	0
H	23	3.274806	-1.658044	1.176311	23	5	0	0	0	0	0
C	24	-5.115277	-0.197794	0.491253	2	15	25	26	0	0	0
C	25	-5.144976	1.241075	0.491431	2	20	24	27	0	0	0
H	26	-6.038777	-0.792213	0.490654	5	24	0	0	0	0	0
H	27	-6.093127	1.795081	0.485630	5	25	0	0	0	0	0
H	28	2.750271	-2.566462	-0.077157	23	5	0	0	0	0	0

YAII085 FROM XRAY CRYSTAL

C	1	0.224767	0.883576	0.586292	2	2	10	11	0	0	0
C	2	-1.038589	0.197247	0.664144	2	1	3	7	0	0	0
C	3	-1.100410	-1.243753	0.752024	2	2	4	18	0	0	0
C	4	-2.312623	-1.877225	0.726006	2	3	5	19	0	0	0
C	5	-3.490172	-1.108306	0.658135	2	4	6	20	0	0	0
C	6	-3.477088	0.252026	0.597159	2	5	7	21	0	0	0
C	7	-2.215840	0.939424	0.638468	2	2	6	8	0	0	0
C	8	-2.215433	2.380074	0.609443	2	7	9	22	0	0	0
C	9	-0.991798	3.017580	0.582966	2	8	10	23	0	0	0
C	10	0.189480	2.275890	0.560522	2	1	9	24	0	0	0
C	11	1.520657	0.091384	0.564776	1	1	12	17	25	0	0
C	12	1.617045	-0.709971	-0.682916	2	11	13	16	0	0	0
N	13	2.559751	-1.726810	-0.805421	9	12	14	32	0	0	0
C	14	2.434084	-2.312353	-1.983817	2	13	15	26	0	0	0
N	15	1.453109	-1.723086	-2.618448	8	14	16	31	0	0	0
C	16	0.941615	-0.710899	-1.821674	2	12	15	27	0	0	0
C	17	2.759636	0.980997	0.754219	1	11	28	29	30	0	0
H	18	-0.192743	-1.822662	0.838096	5	3	0	0	0	0	0
H	19	-2.368826	-2.955330	0.756514	5	4	0	0	0	0	0
H	20	-4.443041	-1.616666	0.654501	5	5	0	0	0	0	0
H	21	-4.399866	0.807668	0.518790	5	6	0	0	0	0	0
H	22	-3.137214	2.942853	0.608258	5	8	0	0	0	0	0
H	23	-0.952853	4.096872	0.579688	5	9	0	0	0	0	0
H	24	1.125156	2.813819	0.521218	5	10	0	0	0	0	0
H	25	1.487184	-0.577276	1.424935	5	11	0	0	0	0	0
H	26	3.032388	-3.130143	-2.357522	5	14	0	0	0	0	0
H	27	0.135326	-0.041281	-2.082269	5	16	0	0	0	0	0
H	28	3.632337	0.484555	0.329907	5	17	0	0	0	0	0
H	29	2.602859	1.934168	0.249259	5	17	0	0	0	0	0
H	30	2.922366	1.155155	1.817839	5	17	0	0	0	0	0
H	31	1.098325	-1.983118	-3.604811	23	15	0	0	0	0	0
H	32	3.284840	-1.997363	-0.052131	23	13	0	0	0	0	0